REMARKS

Claims 21 and 22 are pending in the instant application. Claims 21 and 22 have been rejected. Reconsideration is respectfully requested in light of the following remarks.

I. **Rejection of Claims Under 35 U.S.C. 103(a)**

Claims 21 and 22 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Calabretta et al., in view of Possinger et al. (1995). The Examiner suggests that it would have been *prima facie* obvious for one of skill in the art to modify the method of Calabretta et al. to use gemcitabine in combination therapy since this reference expressly teaches that the non-antisense component may comprise an anti-neoplastic agent useful in the treatment of the particular diseases. The Examiner suggests that motivation is provided by the teaching of Possinger who states that gemcitabine's toxicity profile and single agent activity make it an attractive candidate for combination therapy in breast cancer. The Examiner also suggests that these references provide an expectation of success since Calabretta specifically disclose that combination treatment is desirable and that combinations of agents is more efficient, while Possinger direct the practitioner to combination

therapy specifically using gemcitabine. Applicants respectfully disagree with the Examiner's conclusions regarding this combination of references.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

As acknowledged by the Examiner, Calabretta et al. fail to teach the use of gemcitabine in combination with antisense compounds targeted to ras. Although Possinger et al. teach the use of gemcitabine in cancer, nowhere does this combination of references provide one of skill with an expectation that the combined treatment regimen would be successful in treating or preventing cancer, or at inhibiting proliferation of cancer cells.

Careful review of the Possinger reference reveals that the reference does not provide one of skill with an expectation of success as suggested by the Examiner. In fact, at page 57, the reference teaches that therapy with gemcitabine was <u>not effective</u>

in treatment of breast cancer patients. Then, at page 58, first paragraph, the author admits that the differing results in the two clinical studies led to a third study, the results of which are not presented. Thus, one of skill would not be assured that even gemcitabine therapy by itself was effective as a treatment for breast cancer, let alone gemcitabine in combination with some other product such as an antisense compound. Also relevant to the issue of an expectation of success is a discussion in the Possinger paper at page 58 where the author mentions combining only very specific agents with gemcitabine in order to assure that a favorable toxicity profile will result. It is only this favorable toxicity profile that drives the use of gemcitabine in combination and thus one of skill would only see such a favorable toxicity profile in combination if one performed experiments such as those described in the specification as filed. Then, the conclusions to the Possinger paper state that the use of gemcitabine "deserves further evaluation". Nowhere does this paper teach or suggest, alone or when combined with the other cited art, that gemcitabine in combination with antisense to ras has *in vivo* activity to either inhibit cell proliferation of cancer cells or prevent or treat cancer in an animal. Without such teaching, one of skill would

have to perform experiments such as those described in the specification as filed to determine whether gemcitabine could be used successfully *in vivo*. No data are provided in either of the cited prior art references showing such *in vivo* activity. It is only with the specification in hand that one of skill would understand that these entities, antisense to ras and gemcitabine, could be used successfully and safely in patients to prevent or treat cancer. Accordingly, the combination of cited prior art fails to provide one of skill with such an expectation of success and fails to establish a *prima facie* case of obviousness.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

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favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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Date: July 14, 2003

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